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EXAMINER	
ARCHIE, NINA	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/565,591	KARAOLIS, DAVID K.R.	
	Examiner	Art Unit	
	Nina A. Archie	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 May 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9-21 and 28-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9-21 and 28-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This Office Action is responsive to Applicant's amendment and response filed 5-10-10. Claim 1 has been amended. Claims 1-7, 9-12, 13-21, and 28-30 are pending and under examination.

Claim Rejections Maintained

35 USC § 112

Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. The rejections of claims 1-5, 10-16, and 28-30 under 35 U.S.C. 112, first paragraph failing to comply with the enablement requirement are maintained for the reason set forth in the previous office action. The claim(s) contain subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants arguments filed in response to the 35 U.S.C. 112 first paragraph (enablement), May 10, 2010 is carefully considered, but not found to be persuasive for the reasons below.

Applicant argues:

A) In the examiner's response to applicant's arguments, the examiner states that the 1.132 Declaration by Keith Foster and it appears that the examiner meant to refer instead to the declaration of David Karaolis, as there is no declaration of Keith Foster filed in this application. Applicant statements below are in regards to Examiner's responses in the previous office action that (i) the Staphylococcal aureus experimental results in the present specification do not provide enablement for a gram positive bacteria; (iii) the instant claims are drawn to reducing the virulence of a bacterial pathogen and not limited to the reduction in colonization, concluding that the

experimental data as disclosed in the declaration are not commensurate in scope with the claims; and (iv) the limited number of species disclosed is not deemed to be representative of the genus encompassed by the claims.

Applicants state the disclosures in the specification, the disclosures in Karaolis et al disclose where Staphylococcus aureus colonization and infection in mice were inhibited by c-di-GMP. Applicants' state Ogunniyi et al disclose colonization with Streptococcus pneumonaie as reduced or inhibited by c-di-GMP. Applicants argue experimental support in a total of seven distinct species of bacterial pathogens that span a wide spectrum (since they are all quite different and unrelated) within the genus of bacterial pathogens and nearly evenly divided among gram-negative and gram-positive bacterial pathogens is representative to those of skill in the art would most certainly consider such a number of species spanning a broad spectrum to be representative of the genus of bacterial pathogens. Applicants argue there is no requirement that the colonization and virulence of every bacterial pathogen be inhibited or reduced, but rather one of skill in the art following the guidance set forth in the present specification can reasonably expect and determine routine experimentation that colonization and virulence of most other bacterial pathogens as predicted by Applicant (see the numerous, but non-limiting, examples of bacterial pathogens disclosed in paragraph [0049] of on pages 23-25 of the present specification), would be inhibited or reduced). Applicants argue all nineteen representative examples of cyclic dinucleotides, compounds (I)-(XIX), shown on pages 19-21 of the present specification are in head to tail arrangement and this head-to-tail arrangement is what was intended by the applicant when referring to cyclic dinucleotides. Applicants argue as far as applicant is aware, there is no other arrangement of cyclizing two nucleotides except in a head-to-tail arrangement.

B) Applicant statements below are in regards to Examiner's responses in the previous office action that (vi) the claims are drawn to any cyclic dinucleotide and therefore using any common structure of a cyclic dinucleotide in the methods as claimed is unpredictable based on the teachings of Bowie et al., Science 247:1306-1310 (1990). Applicant re-emphasizes that a small molecule of two nucleotides cyclized into an invariant head-to-tail arrangement bound together by monophosphates is not analogous to

protein structure. Therefore, the unpredictability associated with protein structure as taught by the cited Bowie et al. reference is irrelevant to cyclic dinucleotides, which can be expressed by a common structural formula where variability resides in only the bases and in the substituent groups of the common core structure of two ribose moieties bound in a head-to-tail arrangement by monophosphates.

C) Applicant statements below are in regards to Examiner's responses in the previous office action that (v) declarant's argument that cyclic dinucleotides would have been a matter of routine is not germane because of applicant's disclosure that specific cyclic dinucleotides may act as either agonists or antagonists of c-di-GMP, which applicant states is a property that can be rapidly and readily determined with only routine experimentation using biofilm formation/inhibition assays in microtiter plates, test tubes or flasks, as disclosed in paragraph [0045] and in the examples of the specification; and in the examples of the specification. Applicants argue the specification teaches that the present specification teaches that one of skill in the art can readily determine the effect of c-di-GMP or another cyclic dinucleotide on the biofilm formation of any bacterial pathogen by conducting quick and easy assays in microtiter plates, as exemplified in Example 3, paragraph [00101], pages 53-54. Applicants argue one of skill in the art would only use routine experimentation to conduct the assay by incubating the bacterial pathogen with a cyclic dinucleotide in microtiter plates, then washing and staining the wells to reveal whether or not biofilm formation by the bacterial pathogen was inhibited which would be recognized by those of skill in the art, the use of microtiter plates allows the screening of a multitude of different bacterial pathogens and/or a multitude of different cyclic dinucleotides in microtiter plates with a rapid turnaround period of just a few days. Applicants argue given the guidance provided by the present specification, those of skill in the art would be well enabled to quickly and easily determine, with minimal experimentation that can only be considered routine, the cyclic dinucleotides that would inhibit biofilm formation of biofilm forming bacterial pathogens.

D) Applicant argue in regards to (iii) aforementioned above, those of skill in the art (i.e., in medical/pathogenic bacteriology) would fully understand the interrelationship between the terms "infection", "pathogenicity", "virulence" and "colonization" as

evidenced by the attached pertinent pages of the textbook Thomas Brock, BIOLOGY OF MICROORGANISMS, 3rd edition, Prentice-Hall, 1979 and the attached pages from the Dr. Kenneth Todar's Online Textbook of Bacteriology, 2008, at the website www.textbookofbacteriology.net).

Applicants argue the experimental data in Example 8, page 80 along with Figure 15, of the present specification demonstrating that c-di-GMP inhibits the ability of S. aureus to colonize and infect the mammary gland of mice, is commensurate in scope with both inhibiting or reducing colonization by a bacterial pathogen and attenuating (a usage in the art to mean reduce or weaken) its virulence, thus, the ability of c-di-GMP to inhibit colonization of S. aureus and infection in mice which also means that it attenuated the virulence of S. aureus by in vivo challenge S. aureus in a mouse mastitis model. Applicants argue the correlation between in vitro susceptibility and in vivo effectiveness is not necessary because applicant has directly demonstrated in vivo effectiveness and further supported in declarations filed on October 6, 2008 and September 15, 2009. Applicants state the references listed in the attached Summary Table filed 5/10/2010 disclose a representative number of different gram-positive and gram-negative bacterial pathogens in which c-di-GMP or another cyclic dinculeotide inhibited their ability to colonize and therefore reduced/attenuated their virulence (see references disclosed) and experimental results showing inhibition of colonization and reduce virulence obtained in vivo (see Karaolis et al and Kumagai et al specifically).

Examiners Response to Applicants Arguments:

With regard to Points (A) and (B), the 1.132 Declaration by David Karaolis filed on October 6, 2008 and September 15, 2009 has been fully considered but is not deemed persuasive. Examiner made a editing error by stating Keith Foster instead of David Karolis. The claims encompass any bacterial pathogen for the recited methods. However the specification is limited a method for attenuating the virulence of a single microbial pathogen from *S. aureus or* for inhibiting or reducing colonization by a microbial pathogen from S. aureus in a patient in need thereof, comprising administering to the patient in need an effective amount of c-di-GMP, cGMP and 5'-GMP to attenuate the virulence of, or to inhibit or reduce colonization by, the microbial pathogen. Therefore,

Applicants disclosures in the specification along with references and Karaolis et al and Ogunniyi et al are unpersuasive because Applicants only contemplate the instant invention of administering to the patient in need an effective amount of c-di-GMP or a cyclic dinucleotide with nucleotides in a head to tail arrangement to attenuate the virulence of, or to inhibit or reduce colonization by, the microbial pathogen in the recited methods. Consequently, Applicants have only shown examples that demonstrate a method for attenuating the virulence of a microbial pathogen from *S. aureus or* for inhibiting or reducing colonization by a microbial pathogen from S. aureus in a patient in need thereof, comprising administering to the patient in need an effective amount of c-di-GMP, cGMP and 5'-GMP to attenuate the virulence of, or to inhibit or reduce colonization by, the microbial pathogen. Moreover, the method for attenuating the virulence of a microbial pathogen from *S. aureus or* for inhibiting or reducing colonization by a microbial pathogen from S. aureus is not attenuation or inhibition in the claimed invention against all bacterial pathogens. Therefore one of skill in the art would not reasonably expect and determine routine experimentation of colonization and virulence of most other bacterial pathogens as predicted by Applicant. Furthermore one of skill in the art would not reasonably expect and determine routine experimentation with all examples of cyclic dinucleotides, compounds (I)-(XIX), shown on pages 19-21 in head to tail arrangement because the cyclic dinucleotides disclosed in the specification at paragraphs [0044]-[0046] state c-di-GMP may act to inhibit biofilm formation/colonization/virulence in some bacteria or it may act in the opposite manner and induce or enhance biofilm formation/colonization/virulence in others and also may act as either agonists or antagonists of c-di-GMP which is a property that can be rapidly and readily determined with only routine experimentation using biofilm formation/inhibition assays in microtiter plates, test tubes or flasks, as disclosed in paragraph [0045] and in the examples of the specification. Therefore the Bowie et al reference is relevant stating the unpredictability of utilizing any cyclic dinucleotide in the claimed invention in a method for attenuating the virulence or inhibiting or reducing colonization of any bacterial pathogen. Therefore the rejection is maintained.

With regard to Points (B) and (C), The specification at paragraphs [0044]-[0046] state c-di-GMP may act to inhibit biofilm formation/colonization/virulence in some bacteria or it may act in the opposite manner and induce or enhance biofilm formation/colonization/virulence in others and also may act as either agonists or antagonists of c-di-GMP which is a property that can be rapidly and readily determined with only routine experimentation therefore it one skilled in the art would not would not quickly and easily determine the cyclic dinucleotides for attenuating the virulence or inhibiting or reducing colonization of any bacterial pathogen in the recited methods. Moreover, Applicants have not demonstrated that any cyclic dinucleotide in the recited method is representative as a successful model therefore routine experimentation constitutes an undue burden to one skilled in the art. Therefore Applicants response aforementioned above, in regards to inhibiting biofilm formation of biofilm forming bacterial pathogens are unpersuasive.

With regard to Point (D), although one skilled in the art (i.e., in medical/pathogenic bacteriology) would fully understand the interrelationship between the terms "infection", "pathogenicity", "virulence" and "colonization", the experimental data in Example 8 is not indicative of any empirical data or results displaying a method for attenuating the virulence and for inhibiting or reducing colonization of any bacterial pathogen utilizing the c-di-GMP, or a cyclic dinuclueotide with the nucleotides in a head to tail arrangement only specific for *Staphylococcus aureus (S. aureus)*. Therefore, one skilled in the art would not accept on its face example 8 given in the specification as being correlative or representative of a successful model as claimed. Furthermore, based on the teachings in the specification and the demonstration by Applicant in data presented in the specification of the *in vivo* data demonstrating that c-di-GMP reduces and thus inhibits the ability of *S. aureus* to colonize and infect the mammary gland of mice, one skilled in the art would not expect the in vivo data aforementioned above to be consistent with any method for attenuating the virulence of any microbial pathogen or for inhibiting or reducing colonization by any microbial pathogen in a patient in need thereof, comprising administering to the patient in need an effective amount of c-di-GMP or a cyclic dinucleotide to attenuate the virulence of, or to inhibit or reduce colonization by,

the microbial pathogen. Furthermore one skilled in the art would not except the *in vivo* data provided as directed to the claimed invention and that *in vitro* data does not necessarily correlate with *in vivo* efficacy.

Although the specification contemplates that the same results one would occur *in vitro* would function *in vivo* and vice versa, the specification does not provide any evidence that any of the claimed methods would function *in vivo or in vitro of* the recited method aforementioned above. The issue of correlation is related to the issue of the presence or absence of working examples. Correlation as used herein refers to the relationship between *in vitro* or *in vivo* animal model assays and disclosed or a claimed method of use. An *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a working example, if that example correlates with a disclosed or claimed method invention. Also *in vitro* data does not necessarily correlate with *in vivo* efficacy. If there is no correlation, then the examples do not as constitute working examples. Moreover, the references cited by Applicant that disclose a representative number of different gram-positive and gram-negative bacterial pathogens in which c-di-GMP or another cyclic dinculeotide inhibited their ability to colonize and therefore reduced/attenuated their virulence (see references disclosed) and experimental results showing inhibition of colonization and reduce virulence obtained in vivo (see Karaolis et al and Kumagai et al specifically) is unpersuasive because Karaolis et al and Kumagai et al aforementioned above are only directed at Staphylococcus aureus and Ehrlichia chaffeensis with specific cyclic dinucleotides therefore one of skill in the art would accept these examples as being correlative or representative of a successful model for the claimed invention.

As outlined previously: the specification, while being enabling for a method for attenuating the virulence of a microbial pathogen from *S. aureus or* for inhibiting or reducing colonization by a microbial pathogen from S. aureus in a patient in need thereof, comprising administering to the patient in need an effective amount of c-di-GMP, cGMP and 5'-GMP to attenuate the virulence of, or to inhibit or reduce colonization by, the microbial pathogen, does not reasonably provide enablement for any method for attenuating the virulence of any microbial pathogen or for inhibiting or reducing

colonization by any microbial pathogen in a patient in need thereof, comprising administering to the patient in need an effective amount of c-di--GMP or a cyclic dinucleotide in head to tail arrangement to attenuate the virulence of, or to inhibit or reduce colonization by, the microbial pathogen. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claimed invention.

Nature of the invention. The claims are drawn to any method for attenuating the virulence of a microbial pathogen or for inhibiting or reducing colonization by a microbial pathogen in a patient in need thereof, comprising administering to the patient in need an effective amount of c-di-GMP or a cyclic dinucleotide in head to tail arrangement to attenuate the virulence of, or to inhibit or reduce colonization by, the microbial pathogen.

The breadth of the claims. The method claim is very broad and the product, a cyclic dinucleotides used to administer to a patient is directed to any microbial pathogen. Furthermore the claims are drawn to any method for attenuating the virulence of a microbial pathogen or for inhibiting or reducing colonization of a microbial pathogen in a patient in need thereof, comprising administering to the patient in need an effective amount of any cyclic dinucleotide to attenuate the virulence of, or to inhibit or reduce colonization by, the microbial pathogen. Therefore it is hard for one skilled in the art to determine if any cyclic dinucleotide can be used to attenuate the virulence, inhibit or reduce the colonization or any microbial pathogen in a patient. Since the specification fails to provide particular guidance for any method for attenuating the virulence of a microbial pathogen or for inhibiting or reducing colonization of a microbial pathogen in a patient in need thereof, comprising administering to the patient in need an effective amount of any type of a cyclic dinucleotide to attenuate the virulence of, or to inhibit or reduce colonization by, the microbial pathogen, it would require undue experimentation to practice the invention over the broad scope as presently claimed.

Guidance in the specification/Working Example. The specification discloses in Example 3 (see pp. 49-67), various examples, such as the effect of c-di-GMP on S. aureus biofilm formation (see 00101), the effects of c-di-GMP on S. aureus pre-formed biofilms (00102), c-di-GMP treatment the prevents cell to cell interaction (see 00111), c-di-GMP inhibiting biofilm formation in human and bovine S. aureus (see 00113), the effects of cGMP and 5'GMP on biofilm formation (see 00116), the effect of c-di-GMP treatment on S. aureus pre-formed biofilms (see 00117), and lastly safety and toxicity tests disclosing the treatment of c-di-GMP on mice that indicates to the inventor that c-di-GMP is relatively safe and not toxic (see 00119-00120). There is no showing in the specification that cyclic dinucleotides can be administered to a patient to attenuate the virulence of a microbial pathogen or for inhibiting or reducing colonization by a microbial pathogen. Although the specification gives several examples of a method for inhibiting microbial colonization and pre-formed microbial biofilm by disclosing various examples, such as in vitro studies of the effects c-di-GMP or any cyclic dinucleotides species there of on pre-formed microbial biofilm or biofilm formation and c-di-GMP treatment that prevents cell to cell interaction (see Example 3), the specification fails to show a method comprising administering to the patient in need an effective amount of c-di-GMP or any cyclic dinucleotide to attenuate the virulence of, or to inhibit or reduce colonization by, the microbial pathogen. Furthermore although the specification discloses orally administering c-di-GMP to mice that indicates to the inventor that c-di-GMP is relatively safe and not toxic only contemplates the claimed invention (see 00119-00120). The specification does not give any working example (i.e. challenged mice models or passive immunization approaches). Therefore the specification fails to describe any method for attenuating the virulence of any microbial pathogen or for inhibiting or reducing colonization by any microbial pathogen in a patient in need thereof.

The state of the prior art. The state of the art is unpredictable with regard to administering cyclic dinucleotides to attenuate the virulence of a microbial pathogen or for inhibiting or reducing colonization in a patient. The state of the art questions the correlation between in vivo and in vitro models for treatment of bacterial/microbial

pathogens. For example, Parsek et al proposed four basic criteria to define biofilm-associated infections: (i) Bacterial cell adherence to or association with a surface, (ii) in vivo observation of bacterial cell clusters, (iii) a localized infection pattern, and (iv) increased resistance to antibiotic treatment in the host compared to resistance of genetically equivalent planktonic bacteria. A role for bacterial biofilms in pathogenesis is well established for a number of infections and opportunistic pathogens; for many other infections a link between biofilms and disease has been proposed, but the evidence remains less clear (see Parsek et al 2003. Bacterial biofilms: an emerging link to disease pathogenesis. Annu. Rev. Microbiol. 57:677-701 in its entirety). The state of the art indicate that Reisner et al teach the understanding of *Escherichia coli* biofilm formation in vitro is based on studies of laboratory K-12 strains grown in standard media. The data demonstrate that prevalence and expression of three factors known to strongly promote biofilm formation in *E. coli* K-12 (F-like conjugative pili, aggregative adherence fimbriae, and curli) cannot adequately account for the increased biofilm formation of nondomesticated *E. coli* isolates in vitro. Reisner et al discuss the complexity of genetic and environmental effectors of the biofilm phenotype within the species *E. coli*. Reisner et al teach the results found were a poor correlation between biofilm formation in different media, suggesting that *E. coli* isolates respond very differently to the changing growth and environmental conditions and that this finding emphasizes the relevance and difficulty involved in selecting proper conditions for in vitro biofilm studies which attempt to mirror natural environments in vivo. Reisner et al teach that based the results, in vitro biofilm phenotypes cannot be correlated with the expected virulence phenotypes of the *E. coli* isolates in vivo. Reisner et al further teach that a tremendous impact of environmental conditions highlights the need to develop better biofilm model systems to approximate in vivo situations. Furthermore careful adjustment of the medium composition is an important first step. Incorporation of more adequate surfaces in the experimental design appears to be an additional measure, e.g., by studying biofilm formation directly on eukaryotic cells. However, given that multiple species are present in most environments, we also need to establish models that enable monitoring of possible antagonistic or synergistic interactions between community members (see Reisner et al

2006 Journal of Bacteriology Vol. 188 No. 10 pgs. 3572-3581 see abstract, pg. 3572 column 1 and pg. 3580). Furthermore the art indicates that device related infections are difficult to treat with antibiotics alone and that the minimum inhibitory concentrations (MICs) are not predictive for the therapeutic outcome in either the in vitro or in vivo model. For example the treatment of device related infections between the efficacy of antibiotics and the of drug levels of MICs is poor (see abstract and pg. 1138). Furthermore, the art indicates that the clinical relevance of susceptibility testing has always been questioned because of the difficulty of correlating in vitro susceptibility testing with in vivo clinical effectiveness and that there have always been host/pathogen factors that influence the clinical outcome that cannot be predicted by the results of susceptibility testing (see Stratton 2006 Med. Clin North Am Vol. 6 pgs. 1077-1088 see abstract). The state of the art teach that c-di-GMP is a novel naturally occurring nucleotide identified in prokaryotic systems and has found to be active in eukaryotic systems (see Steinberger et al 1999 FEBS LETTERS Vol. 444 pgs. 125-129 specifically pg. 125). Additionally Bowie et al (Science, 1990, 247:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function, carry out the instructions of the genome and form immunoepitopes. Bowie et al. further teach that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (column 1, page 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (column 2, page 1306). Therefore the art questions whether any type of cyclic dinucleotides would have the same effect on the method as claimed.

Furthermore the art has not shown any method of administering any type of cyclic dinucleotides to attenuate the virulence of any microbial pathogen or for inhibiting or reducing colonization in a patient. The art questions the correlation between an in vivo and an in vitro model. Therefore, given the lack of success in the art. For the reasons set forth supra, the state of the art is unpredictable in regards to administering any cyclic dinucleotide to attenuate the virulence of any microbial pathogen or for inhibiting or reducing colonization in a patient.

In conclusion, the claimed inventions are not enabled for any method for attenuating the virulence of any microbial pathogen or for inhibiting or reducing colonization by any microbial pathogen in a patient in need thereof, comprising administering to the patient in need an effective amount of c-di--GMP or a cyclic dinucleotide in head to tail arrangement to attenuate the virulence of, or to inhibit or reduce colonization by, the microbial pathogen. The state of the art indicates that the clinical relevance of susceptibility testing has always been questioned because of the difficulty of correlating in vitro susceptibility testing with in vivo clinical effectiveness and that there have always been host/pathogen factors that influence the clinical outcome that cannot be predicted by the results of susceptibility testing (see Stratton 2006 Med. Clin North Am Vol. 6 pgs. 1077-1088 see abstract). The art has not shown any method of administering c-di-GMP or any cyclic dinucleotide to attenuate the virulence of any microbial pathogen or for inhibiting or reducing colonization in a patient. Furthermore, the art questions the correlation between an in vivo and an in vitro model. For the reasons set forth supra, the state of the art is unpredictable. There is also a lack of working examples. Although the specification discloses orally administering c-di-GMP to mice that indicates to the inventor that c-di-GMP is relatively safe and not toxic only contemplates the claimed invention. As a result, for the reasons discussed above, it would require undue experimentation for one skilled in the art to use the claimed methods.

Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. The rejection of claims 1-7, 9-21, and 28-30 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement are maintained for the reasons set forth in the previous office action. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants' arguments filed in response to the 35 U.S.C. 112 first paragraph (written description), May 10, 2010 is carefully considered, but not found to be persuasive for the reasons below.

Applicant argues:

A) Applicant believes that this rejection inadvertently includes claims 17-21 because claims 17- 21 are specifically indicated by the examiner on the Office Action Summary page as being allowed. Applicants argue the genus of cyclic dinucleotides is not large and the species of the genus all have two nucleotides with ribose sugar moieties cyclized in a head-to- tail arrangement. Applicants state there are only a limited number of bases (abbreviated in the art as A, G, C, T, U, I) and therefore there are only a limited number of combinations of two bases in the cyclic dinucleotide. Applicants state the chemical structure of c-di-GMP on page 9 of the specification and the 19 other examples of cyclic dinucleotides disclosed on pages 19-21, since the 3'-position on the ribose sugar moiety of a nucleotide is joined to the 5'-position of the partner ribose sugar moiety by a monophosphate (phosphodiester bond of nucleic acids) in a head-to-tail arrangement (no other arrangement is possible), then there is only a single 2'-position (besides the base at the l'- position)on each ribose sugar moiety that can be varied. Applicants state the 2'position can be a hydroxyl (e.g., ribonucleotide), a hydrogen (deoxy ribonucleotide) or a different substituent/moiety, and the variability of cyclic dinucleotides is low, and the genus is on the order of hundreds of species at most. Applicant has described twenty different and specific species of this genus of cyclic dinucleotides in the present specification on pages 19-21. Applicants argue such a number of specifically described specie in the specification is representative of a genus with species that number at most in

the hundreds and would be sufficient for these of skill in the art to recognize that the applicant was in possession of the invention at the time the application was filed. Applicant has taught in the present specification cyclic dinucleotides, with c-di-GMP being the most preferred embodiment, to have the activity of attenuating virulence or inhibiting/reducing colonization of bacterial pathogens. Applicants argue it is only with regard to biofilm formation (and this is only with observations in two species, Vibrio cholerae and Salmonella enteritidis) that applicant discloses the possibility that c-di-GMP may enhance biofilm formation in some bacteria instead of inhibiting/reducing biofilm formation. However, applicant's teaching that, for biofilm formation, c-di- GMP and other cyclic dinucleotides can either enhance or inhibit biofilm formation, shows that the activity (enhancing or inhibiting biofilm formation) of c-di-GMP and cyclic dinucleotides was in applicant's possession.

B) Applicants state determination of whether a cyclic dinucleotide enhances or inhibits biofilm formation is simply reduced to a quick and easy assay that can be performed in microtiter plates with a multitude of different cyclic dinucleotides to determine which specific cyclic dinucleotides will either enhance or inhibit biofilm formation as taught by the specification, thus because such a determination of biofilm inhibitor or enhanced may be needed does not affect the description of the invention to those of skill in the art. Applicants also argue the c-di-GMP and cyclic dinucleotides are expected to attenuate virulence or to inhibit or reduce colonization.

Examiners Response to Applicants Arguments:

With regard to Point (A), Although Office Action Summary stated claims 17-21 are allowed. the Office action on pg. 13 specifically states no claims are allowed. Additionally, claims 17-21 were incorporated in the aforementioned rejection. The specification disclose c-di-GMP reducing the numbers of *Staphylococcus aureus* (*S. aureus)* adhering to hela cells (see Example 3 and Figure 11B or 00119-00120). The specification disclose administering c-di-GMP to mice with an *S. aureus* infection of mastitis and show that treatment shows a significant dose dependent suppressing effect of c-di-GMP on the ability of *S. aureus* to multiply or colonize in the mammary gland (see Example 8 or (00145)). Therefore the specification is limited to a method for attenuating

the virulence of a microbial pathogen from *S. aureus or* for inhibiting or reducing colonization by a microbial pathogen from S. aureus in a patient in need thereof, comprising administering to the patient in need an effective amount of c-di-GMP, cGMP and 5'-GMP to attenuate the virulence of, or to inhibit or reduce colonization by, the microbial pathogen. Additionally the specification is limited to a method for inhibiting *Staphylococcus aureus* and the biofilm formation or for reducing colonization and pre-formed *Staphylococcus aureus* biofilm on a hela surface to an effective amount of c-di-GMP. These disclosures do not provide adequate description of the claimed genus c-di-GMP or cyclic dinucleotides in a head to tail arrangement. The limited number of cyclic dinucleotides the specification is limited to and several other cyclic dinucleotides described in the specification and aforementioned above is not deemed to be representative of the genus encompassed by the instant claims. The specification does not provide adequate description of the claimed genus of c-di-GMP or a cyclic dinucleotide and further comprising a head to tail arrangement. Consequently, the number of species disclosed in the specification is silent with regard to its recited function. Therefore the specification provides insufficient written description to support the genus encompassed by the claim. Therefore, one skilled in the art would not recognize the claimed subject matter in such a way as to convey possession of the presently claimed invention.

With regard to Point (B), one of skill in the art would not reasonably expect and determine routine experimentation with all examples of cyclic dinucleotides, compounds (I)-(XIX), shown on pages 19-21 in head to tail arrangement because the cyclic dinucleotides disclosed in the specification at paragraphs [0044]-[0046] state c-di-GMP may act to inhibit biofilm formation/colonization/virulence in some bacteria or it may act in the opposite manner and induce or enhance biofilm formation/colonization/virulence in others and also may act as either agonists or antagonists of c-di-GMP which is a property that can be rapidly and readily determined with only routine experimentation using biofilm formation/inhibition assays in microtiter plates, test tubes or flasks, as disclosed in paragraph [0045] and in the examples of the specification. Therefore the rejection is maintained.

As outlined previously, the claims are drawn to a vast genus of cyclic

dinucleotides. To fulfill the written description requirements set forth under 35 USC § 112, first paragraph, the specification must describe at least a substantial number of the members of the claimed genus, or alternatively describe a representative member of the claimed genus, which shares a particularly defining feature common to at least a substantial number of the members of the claimed genus, which would enable the skilled artisan to immediately recognize and distinguish its members from others, so as to reasonably convey to the skilled artisan that Applicant has possession the claimed invention. Applicants must adequately describe the genus of cyclic dinucleotides capable of inhibiting or reducing colonization of a bacterial pathogen and attenuating the virulence of a bacterial pathogen.

Applicants have only disclosed the following. The specification disclose c-di-GMP reducing the numbers of *Staphylococcus aureus* (*S. aureus)* adhering to hela cells (see Example 3 and Figure 11B or 00119-00120). Furthermore the specification discloses administering c-di-GMP to mice with an *S. aureus* infection of mastitis and show that treatment shows a significant dose dependent suppressing effect of c-di-GMP on the ability of *S. aureus* to multiply or colonize in the mammary gland (see Example 8 or (00145)). The specification suggests that c-di-GMP can also be used to inhibit biofilm formation of epithelial cell surfaces (see 00119). The specification discloses non-limiting examples of cyclic dinucleotides including c-di-GMP (see 0046).

Therefore the specification is limited to a method for attenuating the virulence of a microbial pathogen from *S. aureus or* for inhibiting or reducing colonization by a microbial pathogen from S. aureus in a patient in need thereof, comprising administering to the patient in need an effective amount of c-di-GMP, cGMP and 5'-GMP to attenuate the virulence of, or to inhibit or reduce colonization by, the microbial pathogen. Additionally the specification is limited to a method for inhibiting *Staphylococcus aureus* and the biofilm formation or for reducing colonization and pre-formed *Staphylococcus aureus* biofilm on a hela surface to an effective amount of c-di-GMP.

The data indicated above does not correlate to the claimed functions set forth in the instant claims and do not provide adequate description of the claimed invention. Applicant has not demonstrated that any cyclic dinucleotide can possess the abilities of

inhibiting or reducing colonization of any bacterial pathogen and attenuating the virulence of any bacterial pathogen as claimed. Furthermore, the limited number of species (for ex. c-di-GMP reducing the numbers of *Staphylococcus aureus* (*S. aureus)* adhering to hela cells) aforementioned above and disclosed in the specification is not deemed to be representative of the genus of cyclic of dinuclucleotides encompassed by the instant claims.

The disclosures do not provide adequate description of the claimed genus c-di-GMP or cyclic dinucleotides in a head to tail arrangement. The specification does not provide adequate description of the claimed genus of c-di-GMP or a cyclic dinucleotide and further comprising a head to tail arrangement. Moreover, Applicant is reminded that adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. Therefore, although the specification discloses examples of cyclic dinucleotides, the specification does not teach any structural limitations and the specification is silent to the correlation of the genus of cyclic dinucleotides and its recited function.

Moreover, the specification, does not disclose distinguishing and identifying features of a representative member of the genus of cyclic dinucleotides to which the claims are drawn, such as a correlation between structure of the cyclic dinucleotides and its recited functions capable of inhibiting or reducing colonization a bacterial pathogen and attenuating the virulence of a bacterial pathogen, so that the skilled artisan could immediately envision or recognize at least a substantial number of members of the claimed genus of cyclic dinucleotides. Moreover, Applicant has not demonstrated that any cyclic dinucleotides aforementioned above is capable of inhibiting or reducing colonization a bacterial pathogen and attenuating the virulence of a bacterial pathogen. Moreover, there is no empirical data reported in the specification at the time of filing showing efficacy of inhibiting a bacterial pathogen and attenuating the virulence of a bacterial pathogen of the function as claimed in the method. Moreover, the specification

is silent with regard to what core structure needs to be present for the cyclic dinucleotide to function as directed in the claim.

Therefore, the specification lacks written description of the instant claimed invention. Therefore, since the specification fails to adequately describe at least a substantial number of members of the genus of to which the claims are based; the specification fails to adequately describe at least a substantial number of members of the claimed genus aforementioned above.

MPEP § 2163.02 states, "an objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed". The courts have decided: The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the "written description" inquiry, whatever is now claimed. See Vas-Cath, Ink's. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993)and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, "'Written Description" Requirement (66 FR 1099-1111, January 5,2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (ld. at 1104).

The Guidelines further state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus.

Therefore, absent a detailed and particular description of a representative number of the members of the genus of cyclic dinucleotides, the skilled artisan could not immediately recognize or distinguish members of the claimed genus of cyclic dinucleotides with the recited activities. Therefore, in accordance with the *Guidelines*, the description of cyclic dinucleotides or c-di-GMP is not deemed representative of the genus of cyclic dinucleotides to which the claims refer and therefore the claimed invention is not properly disclosed.

Applicant is directed to the Guidelines for the Examination of Patent Applications under the 35 U.S.C. 112, first paragraph "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Conclusion

4. No claims are allowed.

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nina A. Archie whose telephone number is 571-272-9938. The examiner can normally be reached on Monday-Friday 8:30-5:00p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner supervisor, Robert Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Nina A Archie

Examiner

GAU 1645

REM 3B31

/Robert A. Zeman/
for Nina Archie, Examiner of Art Unit 1645